DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV - 9 1998

TRANSMITTED VIA FACSIMILE

Bruce A. Williams
Vice President, Marketing and Sales
Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059

RE: NDA 20-785
Thalomid (thalidomide) capsules
MACMIS ID# 7269

Dear Mr Williams:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of press releases for Thalomid (thalidomide), disseminated by Celgene Corporation (Celgene), that are false and misleading and are in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and its implementing regulations. DDMAC specifically refers to press releases for Thalomid dated September 17, 1998 ("Celgene CEO Addresses Biotech Industry on Thalomid Research and Marketing Plans"), September 29, 1998 ("Celgene Announces Plans to Pursue Multiple Myeloma Indication for THALOMID"), and October 1, 1998 ("Celgene launches THALOMID"). DDMAC considers these press releases false and misleading for the following reasons:

Background

The approved product labeling (PI) for Thalomid includes a prominent boxed warning that describes severe, life-threatening human birth defects associated with the use of Thalomid. Specifically, the boxed warning states:

> If Thalomid is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalomid should never be used by women who are pregnant or who could become pregnant while taking the drug. Even a single dose taken by a pregnant woman during her pregnancy can cause severe birth defects.... Major human fetal abnormalities related to thalidomide administration during pregnancy have been documented, and include: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities, facial palsy, eye abnormalities, and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented. Mortality at or shortly after birth has been reported at about 40%.

Because of this toxicity and in an effort to prevent the disastrous consequences of fetal exposure to the drug, Thalomid is approved for marketing only under a special restricted distribution program called the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.). The PI includes three additional boxed warnings describing special information for prescribers, female patients, and male patients about the S.T.E.P.S. program. Under this restricted distribution program, only prescribers and pharmacists registered with the program are allowed to prescribe and dispense Thalomid. In addition, patients must be advised of, agree to, and comply with the requirements of the S.T.E.P.S. program in order to receive Thalomid. It is apparent that the special distribution system and its purpose, as well as the terrible consequences of breeches in that system should be an integral part of every communication about thalidomide.

Press Releases

Promotional materials must provide fair balance. They are in violation of the Act if they fail to present information relating to adverse consequences associated with the use of a drug and fail to include appropriate reference to warnings, precautions, and contraindications. Such disclosures should be presented with a prominence and readability reasonably comparable with the information relating to the effectiveness of the drug. Celgene's three press releases lack fair balance and are therefore misleading.

September 29, 1998 Press Release

This press release, entitled "Celgene Announces Plans to Pursue Multiple Myeloma Indication for THALOMID" fails to present **any** of the information about the significant, potentially fatal, risks associated with the use of thalidomide or the S.T.E.P.S. program (emphasis added).

September 17, and October 1, 1998 Press Releases

These press releases minimize the importance of the serious risk information concerning pregnancy and the risk to the fetus described above and in the PI. The press releases disclose that thalidomide was introduced in Europe in the 1950's as a sedative but was withdrawn in 1962 when it was found to cause birth defects. In addition, the statement "Celgene is aware of the teratogenic potential, and other side effects, of the drug and has undertaken initiatives to minimize the risks associated with its improper use" is included. However, DDMAC considers these limited disclosures inadequate in conveying the extent and severity of the many risks associated with the use of Thalomid.

In addition, the press releases lack fair balance because they fail to disclose other significant risks associated with the use of Thalomid. Thalomid's PI includes warnings regarding several significant risks that are not presented in the press releases, such as peripheral neuropathy

("Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe side effect of treatment with thalidomide that may be irreversible...."), dizziness and orthostatic hypotension, neutropenia ("Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of Thalomid. White blood cell count and differential should be monitored on an on-going basis, and treatment with Thalomid should not be initiated with an absolute neutrophil count of less than 750/mm^3") increased HIV viral load, drowsiness, and somnolence.

The dissemination of promotional materials that minimize or fail to include such highly significant, and potentially fatal, risk information raises significant public health and safety concerns because health care providers who receive these messages may retain the impression that this drug does not carry significant risks with its use.

Violation of 21 CFR 314.550

We remind Celgene that the agency's July 16, 1998, letter to Celgene approving Thalomid under the regulations contained in 21 CFR 314 (Subpart H) also included a specific statement that promotional activities for Thalomid are subject to 21 CFR 314.550. This regulation states that applicants must submit to the agency during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. The three press releases in question were not submitted to the agency as is required by the regulations.

Requested Actions

Celgene should immediately cease dissemination of these materials and all promotional activities that contain the same or similar violations. Furthermore, because the Agency is deeply concerned with the circumstances surrounding these issues, we invite you to meet with us in the near future to discuss our concerns. DDMAC will contact Celgene in order to determine a date for this meeting. Celgene should respond in writing to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857, stating its intent to comply with our request to cease dissemination of these materials. Celgene's response should be submitted no later than November 23, 1998. DDMAC reminds Celgene that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #7269 in addition to the NDA number.

Sincerely,

Mark W. Askine, R.Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications